



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20534
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,109	04/12/2001	Andrew H. Segal	11111/1185	5308

29933 7590 12/31/2002
PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER

ZITOMER, STEPHANIE W

ART UNIT


PAPER NUMBER

1634

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/834,109	Applicant(s) SEGAL et al.	
Examiner S. Zitomer	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Oct 8, 2002
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper Note(s) _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper Note(s) _____ | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Application status

1. Receipt of the Response to Non-Final Office Action filed October 8, 2002 is acknowledged.
2. Objections and rejections not reiterated herein from the previous Office action, paper no. 9 mailed July 16, 2002, have been withdrawn in view of amendments and arguments set forth in the Response. All of applicant's arguments have been fully considered.
3. Regarding the rejection of claims 1-22 under 35 U.S.C. 101 for lack of a specific asserted utility, on reconsideration, the asserted utility of stably transfecting cells with a marker gene such as for the Green Fluorescent Protein (Examples 6 and 9) is acceptable as an asserted utility because of one of skill in the art would have recognized the usefulness of the claimed aptamers and methods for marking cells for sorting or targeting.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection under 35 U.S.C. 112, first paragraph: Lack of enablement

4. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of use, does not reasonably provide enablement for *in vivo* methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with gene therapy encompassed by these claims. There is no working example or description or even a prophetic example of the claimed aptamer covalently linked to a nucleic acid sequence comprising a "biological effector sequence" which, when introduced into an organism by the claimed invention method, effects a specific biological reaction. Examples of "biological effector sequences" include coding and antisense nucleic acids, nucleic acid enzymes and regulatory nucleic acids (page 14, first paragraph, followed by lists of prospective effector sequences). Working examples (pages 30-35) are prophetic with the exception of Example 6 in which antisense effector sequences were shown to inhibit expression of Enhanced Green Fluorescent Protein *in vitro* to a greater degree when conjugated to a human L-selectin aptamer than the aptamer alone. The specification is primarily directed to gene therapy of animals including humans (pages 27-

Art Unit: 1634

29). However, at the time the application was filed, the prior art taught that gene therapy and antisense therapy were inoperative at worst and unpredictable at best. For example, Orkin et al. (1995) reviewed the state of the gene therapy art and reported that, among other problems, "[e]fficacy has not been established for any gene therapy protocol". Notably, in this regard, the specification describes dosage and administration in generalities (pages 28-29) but fails to provide any specific protocol for performing the claimed invention gene therapy methods. The Orkin et al. report also cited "the low frequency of gene delivery to target cells and the lack of definable biochemical or clinical endpoints". Notably, in this regard, the specification fails to identify any biochemical or clinical endpoints of the claimed invention methods. Administration of antisense oligonucleotides has been shown to have unexpected effects as reported in *Science* (Gura 1995). In one example wherein inhibition of B cell activity in culture was attempted the antisense oligonucleotides instead increased B cell activity. This report also cited side effects in animals administered antisense oligonucleotides including death in some instances. While the level of skill in the molecular biology art was high at the time of the claimed invention, Ph.D. or higher, the level of unpredictability was also high as demonstrated by the cited references. Absent the required teaching and/or guidance in the specification, it is clear that the skilled practitioner in the art would have experienced undue experimentation in attempting to practice the claimed invention methods of "introducing a biological effector sequence into a cell" in an organism and "administering said molecule to an organism" and that the disclosure is nothing more than an invitation to experiment. As the Courts have stated,

A specification must be more than an invitation to experiment, i.e., applicant may not require persons skilled in the art to perform undue experimentation to achieve a successful result. See *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1993); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Art Unit: 1634

Response to applicant's arguments

5. Applicant's arguments filed October 8, 2002 have been fully considered but they are not persuasive. The arguments attempt to limit the claimed invention to aptamers and methods for introducing/internalizing a "biological effector sequence" to/in a cell or organism. The statement, "Applicants respectfully submit that a biochemical or clinical endpoint for the claimed invention methods is irrelevant" is tantamount to saying that the claimed invention does nothing. This contradicts "biological effector sequence" in which "effector" clearly requires an activity of the sequence once in the cell. Furthermore, the specification is directed to *in vivo* methods at pages 20-22 and 27-29 and at page 14 specific genes are cited as effector sequences "useful for treating" specific diseases. Clearly, "treating" requires an effect of the "effector sequence". Additionally, applicant's arguments at page 12, lines 5-6, recognize that the "nucleic acid molecules of the present invention modify the function of a...target". While it is agreed that the specification teaches the elements of making the claimed invention outlined at page 8 of the Response, it is pointed out that the specification does not teach how to practice the gene therapy encompassed by the claims. The rejection for lack of enablement may be overcome by limiting the claims to *in vitro* usage.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

6. Claims 2-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The amended claims are confusing in lacking antecedent basis for "the molecule of claim 1 or 2" because it is unclear whether the "molecule" is the "nucleic acid molecule" of the preamble or the "cell surface molecule" in line 3.

(b) Claims 19, 21 and 22 are indefinite due to confusing syntax: In claims 19 and 21 the second "and" (line 5) and in claim 22 the "and" at line 6 is superfluous and should be deleted. In the same vein, the comma after "host cell" at line 4 in claim 19, after "cell" at line 4 in claim 21 and after "host cell" in claim 22 should be deleted.

Art Unit: 1634

(d) Claims 21 and 22 lack antecedent basis for "said bifunctional molecule...of claim 16" because neither claim 16 nor claim 1 or 2 recites "bifunctional molecule". It is suggested to change the terminology or to provide antecedent language.

Rejection under 35 U.S.C. 102(b): Anticipation

7. Claims 1, 3, 5, 7 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gold et al. (5,270,163). Regarding claims 1, 3, 5 and 7, the claimed invention nucleic acid molecule comprising an aptamer linked to a nucleic acid sequence comprising a biological effector sequence wherein the nucleic acid is DNA or RNA and wherein a third nucleic acid sequence comprising a different aptamer may be linked or hybridized to the nucleic acid molecule is disclosed at column 7, lines 12-42 with column 9, lines 15-33, column 11, lines 6-24 and column 13, lines 32-35. The composition of claim 16 comprising the claimed invention nucleic acid molecule of claim 1 and a biologically acceptable carrier is disclosed at column 5, lines 27-31.

Rejections under 35 U.S.C. 102(e): Anticipation

8. Claims 1, 3, 5, 7, 8, 12-14 and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Burke et al. (5,637,459) in view of Gold et al. (5,270,163). Regarding claims 1 and 7, the claimed invention nucleic acid molecule comprising an aptamer covalently linked to a second nucleic acid sequence comprising a biological effector sequence is disclosed at column 15, lines 42-43 (Example 1). Gold et al. is cited to show that the HIV-1 reverse transcriptase aptamers of Burke et al. are biological effectors because they inhibit the enzyme activity (Gold et al., column 42, lines 42-53) and that the "nucleic acid" encompasses DNA and RNA (column 13, lines 32-40). The claimed invention nucleic acid molecule described above is disclosed by Burke et al. also at column 17, lines 14-25 (Example 3) as a chimeric nucleic acid molecule that effects acetyl CoA transfer. Regarding claims 3 and 5, the claimed invention nucleic acid molecule further comprising a third nucleic acid sequence which is a different aptamer covalently linked thereto is disclosed at column 19, lines 1-4 (Example 6). Regarding claim 8, the claimed invention nucleic acid molecule wherein the biological effector sequence encodes a polynucleotide is disclosed at column 17, lines 17-19 as a DNA molecule that encodes an RNA transcript. Regarding claim 12, the claimed invention nucleic acid molecule wherein the biological effector

Art Unit: 1634

sequence comprises a nucleic acid enzyme is disclosed at column 18, lines 42-49 (Example 18) as a chimeric nucleic acid molecule comprising a ribozyme. Regarding claim 13, a nucleic acid comprising a template for assembly of the claimed invention nucleic acid molecule is disclosed at column 17, lines 17-19. Regarding claims 14 and 16-18, a cloning vector comprising the claimed invention nucleic acid molecule, a composition comprising an admixture of the claimed invention nucleic acid molecule, a cell that bears a target for the aptamer thereof and a cell transfected with the claimed invention nucleic acid molecule are disclosed at column 17, lines 31-36 wherein the cells and vectors are in an admixture prior to transfection.

Response to applicant's arguments

9. Applicant's arguments regarding the foregoing rejections over Gold et al. and Burke et al. have been fully considered but they are not persuasive. It is noted that the amended "wherein" clauses are not considered patentable limitations because they recite a future intended use which does not affect the chemistry or structure of the nucleic acid molecule to which the claims are drawn. The arguments that the references do not teach a nucleic acid molecule comprising an aptamer and a biological effector sequence and that the nucleic acid molecules of Gold et al. and Burke et al. do not possess biological activity are specious because "binding" and "modifying" are biological activities that naturally occur in cells and the claims are not limited to any specific "binding" target or "effecting" target. Conversely, features of applicant's invention upon which the arguments rely (i.e., aptamer portion "binds to a target on the cell surface"; biological effector "modifies function of an intracellular component"; aptamer defined in specification as "binding to cell surface molecule") are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is suggested to write claims 1 and 2 in particular, direct functional language which imparts structural limitations, e.g., "aptamer specific for a target cell surface molecule" and "bioeffector sequence selected to effect modification of an internal cellular component".

Art Unit: 1634

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S Zitomer

Stephanie Zitomer, Ph.D.

December 27, 2002

**STEPHANIE W. ZITOMER
PRIMARY EXAMINER**